General Comments on UF-POD

In the hazard identification phase of the risk assessment step, the job of the risk assessment toxicologist is to explore and determine the chemicals likely critical effect at relevant levels of exposure. It is not to explore a chemical's overt toxicities at higher concentrations, since this is an obvious fact. Yes, HCHO can cause lethality at high concentrations and perhaps a host of other effects associated with different organ systems when sufficiently high concentrations exceed the body's ability to detoxify amounts of formaldehyde at the site of entry. However the description of such high dose effects is not the focus of any risk assessment document, and discussion of such effects in EPA's formaldehyde document are superfluous.

With the advent of new risk assessment methods such as benchmark dose, data derived extrapolation factors, and organ-specific RfD and RfCs, the former two on which US EPA has guidelines, the exploration of the critical effect become somewhat more involved. Therefore, exploring or determining the critical effect leading to toxicity and its nearby and/or associated adverse effects is important. EPA does this rather well. Again, however, EPA's extensive literature reviews and write-ups on adverse effects from formaldehyde exposure at concentrations well exceeding the range of the critical effect is not relevant to hazard identification. In fact, EPA's development of RfCs based on respiratory tract pathology and male reproductive toxicity below those from the critical effect of structural changes in the upper respiratory tract is an obvious *non sequitur*.

EPA's focus is to determine a chemical's critical effect based on the assumption that if the critical effect(s) is prevented, then other effects occurring at higher doses or concentrations are also prevented. A complete listing of potential effects from formaldehyde exposure, while perhaps of academic interest, is not relevant to a risk assessment document that supports subsequent rulemaking.

EPA would obviously agree with our comment here since on page xxi they state:

> Based on the current understanding of the toxicokinetics of formaldehyde inhalation exposure (see Appendix A.2), several practical working assumptions were applied to this assessment. Although some uncertainties remain, the organization and analyses in the assessment assume that inhaled formaldehyde is not distributed to an appreciable extent beyond the respiratory tract to distal tissues; thus, it is assumed that inhaled formaldehyde acts via a pathway different from a direct interaction with tissues distal to the portal of entry (POE) to elicit observed systemic effects. Similarly, it is assumed that formaldehyde does not cause appreciable changes in normal metabolic processes associated with formaldehyde in distal tissues. **Thus, studies examining potential associations between levels of formaldehyde or formaldehyde byproducts in tissues distal to the POE (e.g., formate in blood or urine, brain formaldehyde levels) and**

> **health outcomes are not considered relevant here to interpreting the human health hazards of inhaled formaldehyde. [emphasis added]**

Moreover, almost all of the clearly observable adverse effects from formaldehyde exposure are in the range of 1-6 ppm. EPA then conducts dosimetric adjustments to NOAELs in this range, which is not likely relevant given the irritating underlying MOA and a more appropriate dosimeter of Cmax. EPA then applies uncertainty factors to further reduce potential exposures. The net effect of this dual adjustment is to end up at concentrations that are well below likely thresholds for adverse effects, and that otherwise are not capable of penetrating the cellular membrane and being distributed to tissues other than at the site of contact. Table 1 of these comments shows this hidden conservatism.

Specific Comments

Page 1. The mode of action by which toxicity at distal sites, such as bone marrow or reproductive tissues, may occur in response to inhalation of formaldehyde over long periods, also is not known.

> Comment: Yes, but it is known that exposures to such distal sites is unlikely, as multiple publications attest, nor is such exposure relevant as EPA states on page xxi (*v. supra*). This is further supported by a recent case study at the Alliance for Risk Assessment (ARA) workshop series, Beyond Science and Decisions, where formaldehyde was determined not to penetrate cell membranes at concentrations higher than project EPA RfCs.[1]

Page 1. The focus of the assessment is to estimate the risk over background that results from only the exogenous exposure, and the assessment assumes that background incidence of cancer or other health hazard that may potentially be attributed to endogenous formaldehyde is already accounted for in the background.

> Comment: It will thus be reasonable and expected that EPA's dose response assessment values for either cancer or noncancer effects at levels that fall below existing ambient background levels or endogenous levels in humans would not be derived. Furthermore, EPA's values will need to be verified by reference to existing levels of projected disease. For example, EPA's cancer slope factor cannot be seen to project more cancer risk than that which is actually occurring in the human population at current levels of exposure.

Page 2-2. While the RfC is interpreted to be a concentration associated with minimal risk over a lifetime of exposure, a few of the hazards or outcomes, including sensory irritation symptoms, or

[1] See Alliance for Risk Assessment (ARA), Beyond Science and Decisions, Workshop XIII, Final report at https://www.tera.org/Alliance%20for%20Risk/ARA_Dose-Response.htm.

the degree of asthma control, could be relevant to a shorter exposure time frame. The applicability of the osRfC to shorter exposure periods is noted for the relevant hazards.

> Comment: The RfC is interpreted as "an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime." Or otherwise, the RfC is a sensitive human NOAEL. It applies to the whole lifetime and if the critical effect is evoked at exposures less than the whole lifespan then it still applies.

Page 2-10: The regression model adjusted for age, sex and smoking, and the presence of smokers or gas appliances in the home, sources that might contribute to variability in concentrations, were not associated with indoor formaldehyde concentrations.

> Comment: Please further clarify what this sentence means.

Page 2-10: The PODs based on the two controlled human exposure studies were 0.19 and 0.42 mg/m3 (Kulle et al., 1987; Andersen and Molhave, 1983), less than an order of magnitude greater than the BMCL estimated from residential exposure. There is less confidence in the PODs based on these studies because: (1) the study participants were young, healthy volunteers, not representative of the age distribution and health status in the general population; (2) the PODs are based on small sample size, more subject to random variation; and (3) formaldehyde concentrations were high, imposing substantial uncertainty regarding responses at the low tail of the exposure distribution. The utility of the PODs from these two controlled exposure studies may be greater for other, less than chronic, exposure durations (e.g., derivation of an acute RfC).

> Comment: There are a number of problems with this discussion, which inappropriately discount the use of these two clinical human studies with objective formaldehyde measurements over EPA's choice of a residential study with only 2-hours of monitored formaldehyde exposures.

1. First and foremost, the critical effect appears to be the same in both sets of studies, so there is no inherent reason not to use either of the clinical studies;
2. Second, the clinical studies use healthy volunteers, but of course, that is why we have an uncertainty factor for within human variability;
3. Third, each subject in the clinical studies received all concentrations resulting in LESS, not more, variation, which is why EPA adjusted the BMC by a division by 2; and
4. Finally, the lower two concentrations in each of the controlled human studies falls within the range of the human observational study.

> For each of these reasons, and certainly for all of them, EPA's choice of the residential study over the controlled human studies is not rational.

Page 2-10: The exposure-response pattern presented in Hanrahan et al. (1984) is consistent with the overall pattern exhibited when all of the studies of exposure in mobile homes and controlled human exposure studies with dose-response data less than 1 mg/m^3 are graphed together (see Figure 1-3).

> Comment: The prevalence at the lowest concentration of Hanrahan (1984) lies below the lowest prevalence of these other studies. How did this affect the estimation of its BMCL? What would the BMCL be of the collective set of studies? What is the BMD estimated background prevalence for eye irritation in each of these study groups? How does the BMD estimated background prevalence from Hanrahan compare?

Page 2-11. Table 2-3. Summary of derivation of PODs for pulmonary function

> Comment: This appears to be the lowest point of departure for the critical effect in a sensitive population. Thus, an uncertainty factor for within human variability of 1-fold is the appropriate judgment. That this is the correct choice of factor is supported by footnote "c" of this table, specifically, "A BMR of 10% reduction in PEFR was selected as a cut-off point for adversity." And further supported by statements of the American Thoracic Society in this same footnote. See also Table 2 of these comments.

Pages 2-15,16: Table 2-4. Summary of derivation of PODs for allergies and current asthma based on observational epidemiology studies

> Comment: The choice of LOAELs for studies in this table, rather than a BMD is perplexing, and not consistent with current EPA guidelines, unless of course this was tried and the modeling failed. Why not develop a BMDL on the basis of the raw data for all of these studies, as what was done for Venn et al. (2003)?[2]

> Comment: We do not understand the choice of LOAEL in the Matsunaga et al. (2008) study. None of the individual ORs are statistically significant, correct? Nor is the trend significant. Significance is only wrought when all lower groups are combined when compared with the high group, and inexplicitly, the LOAEL is assigned a lower value in the range of this high dose range. This appears to be fishing for an answer that is not otherwise present. If our EPA colleagues think that something is going on in this study, and it well may be, then consider conducting a BMD on the raw data, as previously suggested.

> Comment: Were those exposed in the Krzyzanowski et al (1990) study above 0.11 also

[2] For an example on how to do this please see: https://tera.org/sseus/iternew/chemdetail.php?rec=METHYLMERCURY&hide1=0000000000000256&term1=methyl&kind1=name&orgs11=0&stype1=startwith&start1=.

responders? If so, or if unknown, then the average should include the upper part of the range. Otherwise, you are missing the most influential part of the data.

Comment: As EPA staff know well, assigning a NOAEL to a study that does not otherwise have a LOAEL is reasonable, but using this NOAEL as a POD without reference to other information, such as a LOAEL for a comparable effect is a similar study, is not reasonable.

Page 2-16. The analyses by Annesi-Maesano et al. (2012) were adjusted for age, gender, passive smoking, and paternal or maternal history of asthma or allergic disease; thus, minimal impact by confounding is likely. Therefore, both the study and the POD based on the NOAEL in Annesi-Maesano et al. (2012) is viewed with high confidence.

Comment: This study was done in over 6000 children and thus can be used to forgo the usual uncertainty factor for within human variation. A value of 1-fold is appropriate here.

Page 2-17. However, there would be considerable uncertainty in a POD derived from these studies, identified as a LOAEL, given the dichotomous analyses used to examine associations and the wide variability in exposure concentrations within each of these studies (e.g., 0.1 to >0.5 mg/m3). Therefore, PODs were not determined using the occupational studies.

Comment: Perhaps this is a correct judgment, but what were the effects seen in these studies? If minimally adverse, then the LOAEL can be estimated from this range. EPA should not have a problem with doing this, since they estimated NOAELs from ranges in other human studies already discussed.

Page 2-19. Table 2-5. Summary of derivation of POD for squamous metaplasia based on observations in F344 rats (Kerns et al., 1983). Specifically, the adjusted human exposure concentration of 0.086 mg/kg-day/m^3.

Comment: This value is lower than the occupational range of exposure found on page 2-17 of 0.1 to >0.5 mg/m^3. What kind of effects did the occupational studies find? Do they match the effects projected here, that is, 10% or a lower value of squamous metaplasia?

As previously mentioned, if EPA develops RfCs for effects that are clearly ABOVE the critical effect, but which are otherwise lower than the RfC of the critical effect, then this is an obvious *non sequitur*. EPA should not spend time on doing anything like this.

Page 2-20. Squamous metaplasia was also observed in humans exposed to formaldehyde levels between 0.1 and 2.5 mg/m^3 (see Section 1.2.4).

Comment: So squamous metaplasia was observed in humans between 0.1 and 2.5 mg/m^3, yet EPA projects the $BMDL_{10}$ in humans based on rat data to be 0.086 mg/kg-day/m^3 in an earlier section. Was the frequency in humans in this study comparable to this projected BMDL from rats? Was this frequency dose-related? The use of the rat data may be justified, but the BMDL needs to be consistent the findings in humans.

Page 2-22. Table 2-7. Adjusted time-weighted average formaldehyde exposures for Taskinen et al. (1999), Section "B", Background formaldehyde (ppb) value of 0.026 ppb.

Comment: From where did this value come? Background in Finland is 21.4 ppb as per page 2-21.

Page 2-23. Table 2-8. Summary of derivation of PODs for reproductive toxicity in females, where referent population is stated to have zero exposure.

Comment: Background in Finland is 21.4 ppb. Please work this value into all of the exposures in this table and recalculate the POD. Why not conduct a BMD analysis on the raw data?

Page 2-24. …a subacute endpoint was not considered an appropriate basis for a chronic RfC when data from longer-term exposure were available from the same study.

Comment: EPA is confusing its terminology here. "Subacute" refers to toxicity that is less than frank. It does not refer to acute or short-term length of exposure. And yes "subacute" effects are used all the time in determination of the critical effect. More to the point, however, was a BMD analysis attempted for the 13-week exposure? And more generally, why is EPA interested in these clearly-not-critical effects?

Page 2-26. A factor of 3 was then applied to account for residual uncertainties in interspecies extrapolation from the two candidate RfCs for respiratory pathology and the two cRfCs for reproductive toxicity in males derived from rat studies.

Comment: This judgment of 3-fold for toxicodynamic differences is likely to be correct, but EPA should do its due diligence using its EPA (2014)[3] Data-Derived Extrapolation Factor guidance to determine whether sufficient data exist to replace this default value. As EPA knows, the choice of a factor here depends on the underlying MOA. If the MOA is expected to be similar in rats and humans, then this toxicodynamic factor of 3 may not be needed.

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[3] U.S. Environmental Protection Agency (EPA). 2014. Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation. EPA/100/R-14/002F. September.

Page 2-26,7. For Venn et al. (2003), a UFH of 3 was used because the POD was based on the degree of asthma control in children with asthma, a highly sensitive group. (A UFH of 1 was considered but not used because the number of individuals in the two higher exposure groups was relatively low (n = 31–35), and likely did not characterize all possible human variability.)

> Comment. This is not logical judgment, nor consistent with prior EPA decisions. The RfC is a sensitive subgroup NOAEL. This is what EPA has in hand with this study, so a factor of 1 is supportable. See Dourson et al. (2001) for examples of EPA prior selections of uncertainty factor when using human data.[4] See also Table 2 of these comments.

Page 2-27. For the POD for decreased peak expiratory flow rates (PEFRs) among children from Krzyzanowski et al. (1990), a UFH of 3 was used with support from the model results reported by the authors.

> Comment: If this study included asthmatic children, then the uncertainty factor for within human variability can be reasonably judged to be a value of 1. See also Table 2 of these comments.

Page 2-27. However, a UFH of 1 was not used because susceptibility among subsets of the study population was not specifically assessed.

> Comment: Once again, EPA is not following its own logic nor past experience. A NOAEL in a group of ~6700 children will include sensitive individuals. If you have this NOAEL, you have the RfC. See Dourson et al. (2001) for earlier examples of RfDs and RfCs developed by EPA from human data. See also Table 2 of these comments.

Page 2-27. For current asthma prevalence among children with residential exposure (Krzyzanowski et al., 1990), a UFH of 10 was used because susceptibility among subsets of the population was not specifically assessed, and the precision of the NOAEL was lower compared to Annesi-Maesano et al. (2012).

> Comment: The uncertainty factor for within human variability can be reasonably judged to be a value of 1 for a group of ~300 children. EPA has the NOAEL in a sensitive subgroup. See also Table 2 of these comments.

Page 2-28. For the cRfC for sensory irritation in adult (and teenage) populations (residential exposures) in Hanrahan et al. (1984), a UFH of 10 was used.

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[4] Dourson, M., M. Andersen, L. Erdreich and J. MacGregor. 2001. Using human data to protect the public's health. Regul Toxicol Pharmacol. 33(2): 234-256.

Comment: UFH for sensory irritation is not following EPA logic or prior judgments. Since minimal sensory detection/irritation is a perceived effect that does not change the form or function of humans, then this is not an adverse health effect and no uncertainty factors should be applied. However, if this sensory irritation at the point of contact was judged to be adverse, then little-to-no kinetic differences among individuals are expected. A factor of 3 would be the better judgment and would be for potential toxicodynamic differences among individuals for an adverse effect. See also T Table 2 of these comments.

Page 2-28. …a factor of 10 was applied to account for variation in the broader human population not represented by occupationally exposed groups or participants in controlled human exposure studies who met the eligibility criteria.

Comment: EPA staff seems to be missing the point of this factor, which represents both toxicokinetic and toxicodynamic variability among individuals. Sensory irritation, especially at the point of contact, is not expected to have kinetic variability. A factor of 3-fold for dynamic variability is the appropriate judgment, if the endpoint rises to the level of adversity. It is also important to recognize the human sensory irritation studies are not adverse effect studies in humans, as such studies would be deemed unethical, but have not been judged as such. See also Table 2 of these comments.

Page 2-28. A BMR of 5% was selected for the POD identified using the Venn et al. (2003) study for effects on degree of asthma control.

Comment: Please justify this departure from the default value of BMDL 10. Also please recognize that if lower BMRs are used, then this may impact the selection of the overall uncertainty factor for within-human variability. See Haber et al. (2018) for a discussion of this. Specifically, Figure 2 on page 6 and associated text on pages 6 & 7.[5]

Page 2-28. A factor of 10 was applied to the two PODs for male reproductive toxicity to approximate the potential effect of lifetime exposure, as these effects are not necessarily dependent on a specific exposure window and they are expected to worsen with continued exposure (Ozen et al., 2005; Ozen et al., 2002).

Comment: These studies cannot be used to develop RfDs with any confidence. Why?

- They do not have the required number of animals per dose group as per numerous EPA guidelines and practice;

[5] Haber, Lynne T., Michael L. Dourson, Bruce C. Allen, Richard C. Hertzberg, Ann Parker, Melissa J. Vincent, Andrew Maier & Alan R. Boobis (2018): Benchmark dose (BMD) modeling: current practice, issues, and challenges, Critical Reviews in Toxicology, DOI: 10.1080/10408444.2018.1430121.

- They do not follow GLP guidelines;
- They do not take recommended measurements (like absolute organ weight). EPA has traditionally considered both absolute and relative weights in its adversity judgments (see EPA's IRIS for numerous examples).
- Moreover, formaldehyde is not expected to reach these target organs at low concentrations at sites different than the point of entry, **AS EPA STATES ON ITS PAGE XXI**.[6]
- Nor are the use of these studies consistent with recent findings of an Alliance for Risk Assessment (*ARA*) international workshop (*ARA*, 2022, report just published) where formaldehyde was used to demonstrate a new approach to dosimetry, showing that low concentrations of exogenous formaldehyde are not to be able to penetrate the cell nucleus at the site of contact.

Page 2-28. A factor of 3 was applied to the respiratory tract pathology POD from Kerns et al. (1983) because it was based on 18-month exposure data from that rodent study in lieu of the 24-month exposure data available in the same study.

> Comment: Although this study can be used to develop an RfC, the critical effect of formaldehyde is clearly irritation that occurs before metaplasia. The fact that an RfC developed from metaplasia is lower than several of the RfCs developed from irritation demonstrates metaplasia's poor choice for evaluation. If irritation is a precursor to metaplasia, then protecting against it will protect against this metaplasia as well.

Page 2-29. For one study in a human population, a UFS of 3 was applied to the POD. Matsunaga et al. (2008) evaluated the occurrence of atopic eczema during the past 12 months in a group of pregnant women and analyzed this outcome in relation to formaldehyde concentrations measured in their homes, which is a less-than-lifetime window of vulnerability.

> Comment: Was the effect associated with the pregnancy? If so, a 12-month exposure is a sufficient length of time for pregnancy in any woman and the 3-fold factor is not needed.

Page 2-29. The formaldehyde database is not considered complete, as important questions remain regarding the potential for formaldehyde inhalation exposure to cause reproductive and developmental toxicity and nervous system effects (both of which demonstrate an incomplete evidence base with methodological limitations).

> Comment: This is a misjudgment by EPA staff. The underlying MOA for formaldehyde as a direct acting toxicant necessitates its getting to the target organ at low

[6] EPA's quote on page xxi is: "Thus, studies examining potential associations between levels of formaldehyde or formaldehyde byproducts in tissues distal to the POE (e.g., formate in blood or urine, brain formaldehyde levels) and health outcomes are not considered relevant here to interpreting the human health hazards of inhaled formaldehyde."

concentrations. This is not expected to occur with organs at sites different than the point of entry, **AS EPA STATES ON ITS PAGE XXI,** nor from recent findings of an Alliance for Risk Assessment (*ARA*) international workshop (*ARA*, 2022, report just published). See previous footnotes.

However, EPA's choice of a 1-fold uncertainty factor is appropriate here. This is because while EPA has routinely judged this factor to be appropriate when certain studies are missing from the database (e.g., Dourson et al., 1992; EPA, 2002)[7], it also has judged that certain studies are not needed when it can be ascertained that the underlying tissues will not be impacted. EPA's Integrated Risk Information System (IRIS) has numerous examples of this latter judgment. Formaldehyde's inability to be transported to distal sites in the body from the point of entry at low concentrations would easily fit into EPA's previous judgments.

Page 2-33. The POD is based on formaldehyde measurements in the participants' homes (1-hour sampling period in two rooms).

Comment: So EPA staff judges that "1-hour sampling period in two rooms" associated with effects in 61 folks is a better choice of POD than two control human exposure studies tied to these same effects in 26 folks. EPA seriously needs to relook at this judgment. The clinical human studies have control exposures and effects tied directly to these exposures. The residential study has neither.

Page 2-34. Data from a study in a residential population exposed over multiple years was used to calculate a cRfC for pulmonary function of 0.007 mg/m3 (Krzyzanowski et al., 1990).

Comment: Were any of the children in this study considered to be asthmatics? If so, then a NOAEL from this study would be, in effect, the RfC, and a UFH of 3-fold is not needed. See also T Table 2 of these comments.

Page 2-34. Both PODs were based on NOAELs and are interpreted with *high* confidence. In particular, the large study of children (n = 6,683) by Annesi-Maesano et al. (2012) was able to address the variability in susceptibility that would be anticipated within a population.

Comment: Sensitive children were very likely present with an "n" of 2200 at the POD, so

[7] Dourson, M.L., L.A. Knauf, and J.C. Swartout. 1992. On Reference Dose (RfD) and Its Underlying Toxicity Data Base. Toxicology and Industrial Health. 8(3): 171-189.

U.S. Environmental Protection Agency. 2002. A review of the Reference Dose (RfD) and Reference Concentration (RfC) processes. Risk Assessment Forum. EPA/630/P-02/002F, December.

a UFH of 1 is supported. See also Table 2 of these comments.

Page 2-34. There were three cRfCs developed for asthma based on the endpoints, current asthma, and degree of asthma control (Annesi-Maesano et al., 2012; Venn et al., 2003; Krzyzanowski et al., 1990).

Comment: Krzyzanowski has an "n" of 298 children, with 24 at the POD. A UFH of 1 is supportable. See Dourson et al. (2001) for examples of previous EPA judgments of this uncertainty factor with human data (see previous footnote). See also Table 2 of these comments.

Page 2-34. Although the effect estimates derived by Venn et al. (2003) were less precise because of relatively small group sizes, the POD derived from Venn et al. (2003) reflects the response among a susceptible population, asthmatic children.

Comment: A BMCL in a sensitive population is the equivalent of an RfC. The UFH can be judged as 1. The fact that this is a BMCL5 also supports the lower uncertainty factor as per Haber et al. (2018) (see previous footnote). See also Table 2 of these comments.

Page 2-41. Research in experimental animals with regard to two health effects, respiratory tract pathology and male reproductive toxicity, indicates that the proposed overall RfC may not be protective against these hazards.

Comment: But how can EPA say this based on their prior statement that effects at sites distant from point of entry are unlikely to see any formaldehyde after low concentrations (see previous footnotes)? These lower values are an anomaly based on the use of larger uncertainty factors. They are clearly not based on effects that are critical and their analysis is superfluous.

Page 2-41. The potential for formaldehyde to adversely affect the nervous system, female and male reproduction, as well as development are not well studied, and the systemic effects of inhaled formaldehyde are not well understood.

Comment: However, the systemic distribution of formaldehyde, or its lack, is well understood. Moreover, recent findings by an international workshop confirm these findings (see previous footnote). Exogenous formaldehyde at low concentrations is not distributed to distal sites and cannot even penetrate the nucleus of the cell at the site of contact.

Page 2-42. An inhalation RfC for formaldehyde has not previously been derived. In 1990, an oral reference dose (RfD) of 0.2 mg/kg-day was developed. This value was based on reduced weight gain and histopathology (primarily of the gastrointestinal system) in Wistar rats during a 2-year

bioassay in which formaldehyde was administered in the drinking water (Til et al., 1989).

> Comment: The oral histopathology was associated in part with the high concentration irritant effects on the oral mucosa by formaldehyde, similar to irritant effects of formaldehyde after inhalation exposure. A roughly comparable RfC based on this oral RfD would be (0.2 mg/kg-day x 70 kg ÷ 20 m3/day = 0.7 mg/m3 or 100 fold higher than the RfC of 0.007 mg/m^3 currently estimated in this draft. Is this 100-fold difference consistent with EPA's understanding of formaldehyde's critical effect? If not, should we expect oral and inhalation irritation differences of 100-fold?

The Bottom Line:

EPA should focus on the area of critical effect and not belabor effects that are clearly well advanced in formaldehyde's underlying MOA. For example, estimating an RfC for a pathological endpoint that only occurs well above a NOAEL or BMDL for tissue irritation is non-sensical. Furthermore, EPA has some exquisite human data in hand including data in sensitive subgroups. EPA needs to recognize that a NOAEL or BMDL for such data are, in effect, the RfC. In such cases, no additional uncertainty factors are needed for within-human variability, as readily demonstrated by prior EPA judgments found on its Integrated Risk Information System (IRIS).